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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/001,281 | 11/30/2001 | Wen-Jen Hwu | 9516-026-999 | 2126 |

20583 7590 05/14/2003

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| EXAMINER |
|---|
| OSTRUP, CLINTON T |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1614 | 8 |

DATE MAILED: 05/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/001,281 | HWU, WEN-JEN | |
| | Examin r | Art Unit | |
| | Clinton Ostrup | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the corresp ndence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *3/5/03* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *22-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-45* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

Claims 1-45 are pending in this application.

### *Priority*

Priority to U.S. Provisional Application Number 60/250,130, filed December 1, 2000, has been acknowledged.

### *Election/Restrictions*

Applicant's election with traverse of Group I, claims 1-21 in Paper No. 7 is acknowledged. The traversal is on the ground(s) that a search and examination of the entire application could be made without serious burden because each of the claims comprises temozolomide and thalidomide. This is not found persuasive because Group I is drawn to methods of treating cancer, Group II is drawn to methods of reducing or preventing an adverse effect associated with the administration of temozolomide, Group III is drawn to a methods of increasing the therapeutic efficacy of temozolomide, Group IV is drawn to a pharmaceutical composition and kit comprising said composition, Group V is drawn to a method of increasing the dosage of temozolomide that can be safely and effectively administered to a patient and Group 6 is drawn to methods or reducing or preventing the adverse effects associated with the administration of thalidomide.

These inventions are distinct for the reasons set forth in the previous Office Action, mailed February 5, 2003, Paper No. 6. Moreover, a complete understanding of the biological and biochemical mechanisms of action of chemotherapeutic agents are not fully known, thus for each invention listed above, a search and examination must be preformed not only on the presence or absence of thalidomide and temozolomide, but

also on the obviousness of combining other anti-angiogenic and cytotoxic agents for each of the claimed inventions.

The requirement is still deemed proper and is therefore made FINAL.

Applicants traverse of the Election of Species Requirement has been noted. It should be remembered that the purpose of an election of species requirement is to simplify the search and issues considered during prosecution, and that because this is so, the ultimate allowance of a generic claim will encompass all additional species within the scope of the allowed genus. Stated alternatively, the purpose of an election of species requirement, as opposed to a restriction between claim groups, is to reduce the burden on the examiner during prosecution only; a full search is merely postponed until allowance of the generic claim.

Thus, currently the search and examination of claims 1-21 as they read on metastatic brain cancer, the elected species.

The requirement is still deemed proper and is therefore made FINAL.

Claim 22-45 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arance et al., Three-arm Phase II study of temozolomide (TMZ) in metastatic melanoma (MM): preliminary results and further in view of Newton Novel Chemotherapeutic Agents for the Treatment of Brain Cancer.

Arance et al., teach that temozolomide was combined with thalidomide and administered to patients with metastatic melanoma and that the treatment was active and well tolerated. See: abstract.

Although the primary reference teaches the combination of both temozolomide and thalidomide for the treatment of metastatic melanomas, the reference lacks the specific teaching of using said combination for treating brain cancer, the elected species, and the specific dosage ranges and schedules as claimed instantly.

Newton teaches Temozolomide as a drug that has shown significant activity and excellent tolerability in clinical trials against both adult and pediatric malignant gliomas. The secondary reference teaches that temozolomide pharmacokenetics appear to be

linear and that single doses can be administered over a range of 200-1200 mg/m$^2$ with an optimal schedule continuous schedule of 75 mg/m$^2$/day for seven weeks.

Newton teaches thalidomide as an angiogenesis inhibitor drug which has been shown to have activity at a dosage rate of 800-1200 mg/day and that thalidomide may be combined with other antineoplastic agents such as carboplatin.

Newton teaches that temozolomide has the widest range of activity as a single agent, but it may be more efficacious in combination with other cytotoxic drugs such as BCNU or cisplatin or with newer agents like marimistat or thalidomide. See: abstract; page 2815 – page 2818, col. 1, line 3; page 2820, col. 1, first full paragraph – page 2821, col. 2, line 13; page 2822, col. 2, first full paragraph – page 2824, col. 2, end of last paragraph.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to have used the combination of temozolomide and thalidomide as taught by Arance et al. for the treatment of brain cancers as suggested by Newton because of the reasonable expectation of obtaining a method of treating brain cancer using a combination of drugs which have been taught to have activity against brain cancer independently and have been suggested for use together because of their different mechanisms of action (i.e. temozolomide is a DNA alkylating agent and thalidomide blocks angiogenesis induced by VGEF).

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Clinton Ostrup whose telephone number is (703) 308-3627. The examiner can normally be reached on 8:00am - 4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel can be reached on (703) 308-4725. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Clinton Ostrup
Examiner
Art Unit 1614

Frederick Krass
Primary Examiner
Art Unit 1614

May 12, 2003